Enantioselective Synthesis of 1,2,4-Triazolines
Catalyzed by a Cinchona Alkaloid-Derived Organocatalyst

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Supporting Information

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General Methods and Materials:

All reactions were carried out under air using anhydrous solvents. Catalyst 5, catalyst 6, and catalyst 7a-d were prepared according to literature procedures. Azlactones were prepared according to reported procedures. All other reagents were purchased and used without further purification unless specified otherwise. Solvents for chromatography were technical grade and distilled prior to use. Flash chromatography was performed using 200-300 mesh silica gel (Qingdao Haiyang Chemical HG/T2354-92) with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed using Huanghai silica gel plates with HSGF 254. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or appropriate stains. $^1$H NMR and $^{13}$C NMR data were recorded on Bruker 400M or 500M nuclear resonance spectrometers unless otherwise specified. Chemical shifts (δ) in ppm are reported as quoted relative to the residual signals of chloroform (1H 7.26 ppm or $^{13}$C 77.16 ppm). Multiplicities are described as: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet); and coupling constants (J) are reported in Hertz (Hz). $^{13}$C NMR spectra were recorded with total proton decoupling. Chiral HPLC was recorded on a Shimadzu LC-20A spectrometer using Daicel Chiralpak OD-H, OJ-H, AD-H, AS-H, IA, or IB columns (250 x 4.6 mm). HRMS (ESI) analysis was performed by The Analytical Instrumentation Center at Peking University; Shenzhen Graduate School and the data were reported with ion mass/charge (m/z) ratios as values in atomic mass units.
Preparation of cinchona alkaloid-derived catalysts

General procedure for the synthesis of catalyst 7 from Carboxylic Acid Chlorides and (S)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)-methanamine.\(^6\)

A solution of (S)-((1S,2S,4S,5R)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)-methanamine, prepared from quinine following the literature procedure,\(^2\) (488 mg, 1.5 mmol) in 10 mL dry dichloromethane and 2 mL triethylamine was cooled to 0°C. The corresponding carboxylic acid chloride (1.8 mmol) in 2 mL dichloromethane was added dropwise. After the reaction mixture was stirred overnight at room temperature, another 10 mL dichloromethane was added, the reaction was washed three times with aqueous Na\(_2\)CO\(_3\) solution and dried over Na\(_2\)SO\(_4\). The volatile solvent was removed and the product was purified by silica gel flash chromatography (ethyl acetate / methanol).

Catalyst 7d:
85% yield, white powder. \(^{27,8} [\alpha]_D = -67^\circ\) (c = 0.1, CHCl\(_3\)); \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta 8.77\) (d, \(J = 4.6\) Hz, 1H), 8.26 (s, 2H), 8.08 (d, \(J = 9.2\) Hz, 1H), 8.01 (s, 1H), 7.94 (s, 1H), 7.72 (d, \(J = 2.2\) Hz, 1H), 7.49 – 7.40 (m, 2H), 5.45 (s, 1H), 4.03 (s, 3H), 3.31 (dd, \(J = 13.6, 10.0\) Hz, 1H), 3.24 (s, 1H), 3.11 (s, 1H), 2.81 – 2.71 (m, 1H), 2.53 (dd, \(J = 13.7, 2.7\) Hz, 1H), 1.78 (s, 3H), 1.71 (s, 2H), 1.63 – 1.55 (m, 1H), 1.53 – 1.42 (m, 2H), 1.33 – 1.25 (m, 2H), 1.05 (dd, \(J = 13.4, 6.7\) Hz, 1H), 0.85 (t, \(J = 7.3\) Hz, 3H); \(^{13}C\) NMR (CDCl\(_3\), 100 MHz): \(\delta 164.5, 158.1, 147.4, 144.7, 136.0, 132.5, 132.1, 131.8, 131.5, 128.3, 127.7, 127.0, 125.0, 124.3, 121.8, 121.6, 118.8, 101.8, 57.5, 55.6, 41.0, 37.0, 28.4, 27.3, 26.0, 25.0, 11.9\); HRMS (ESI) Calcd. for C\(_{29}H\(_{30}\)F\(_6\)N\(_3\)O\(_2\) ([M+H]+): 566.2242; Found: 566.2222.

Electronic Supplementary Material (ESI) for Chemical Communications
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Condition screening:

Screening for different catalysts, solvent, catalyst loading, additive, concentration and temperature.

Table S1. Catalyst screening in toluene at r.t.\(^a\)

<table>
<thead>
<tr>
<th>Catalyst</th>
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<tr>
<td>DHQ</td>
<td>-31%</td>
</tr>
<tr>
<td>DHQD</td>
<td>18%</td>
</tr>
<tr>
<td>Q-Pv</td>
<td>-27%</td>
</tr>
<tr>
<td>QD-Piv</td>
<td>-16%</td>
</tr>
<tr>
<td>Q-Ph</td>
<td>-13%</td>
</tr>
<tr>
<td>DHQ-D-OH</td>
<td>-8%</td>
</tr>
<tr>
<td>DHQ-QN</td>
<td>-43%</td>
</tr>
<tr>
<td>DHQ-QN-H</td>
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</tr>
<tr>
<td>DHQ-QN-H-Ph</td>
<td>-46%</td>
</tr>
<tr>
<td>DHQ-QN-H-Ph</td>
<td>-43%</td>
</tr>
<tr>
<td>(DHQ)_2AQN</td>
<td>13%</td>
</tr>
</tbody>
</table>

\(^a\): reactions were carried out using 1 (0.1 mmol), DIAD (0.1 mmol), and catalyst (0.01 mmol, 10 mol%) in toluene (1 mL) at 25 °C for 12 hours, unless specified otherwise. \(^b\): the ee value was determined by chiral HPLC analysis.
Table S2. Catalyst screening in TBME at r.t.

<table>
<thead>
<tr>
<th>Catalyst Scaffold</th>
<th>Reaction Conditions</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>DHQ scaffold</td>
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</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>-55%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-63%</td>
<td></td>
</tr>
<tr>
<td>cyclohexane diamine scaffold</td>
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<td>8%</td>
</tr>
<tr>
<td></td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td></td>
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<tr>
<td>Other scaffold</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-4%</td>
<td></td>
</tr>
</tbody>
</table>

*: reactions were carried out using 1 (0.1 mmol), DIAD (0.1 mmol), and catalyst (0.01 mmol, 10
mol%) in MTBS (1 mL) at 25 °C for 12 hours, unless specified otherwise. b: the ee value was determined by chiral HPLC analysis.

Table S3. Solvent screening at r.t.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Ee%</th>
<th>Solvent</th>
<th>Ee%</th>
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<tr>
<td>1 MTBE</td>
<td>-83</td>
<td>9 iPr$_2$O</td>
<td>-91</td>
</tr>
<tr>
<td>2 DCM</td>
<td>-74</td>
<td>10 2-MeTHF</td>
<td>-72</td>
</tr>
<tr>
<td>3 MeCN</td>
<td>-29</td>
<td>11</td>
<td>-89</td>
</tr>
<tr>
<td>4 Et$_2$O</td>
<td>-91</td>
<td>12 Dioxane</td>
<td>-83</td>
</tr>
<tr>
<td>5 Toluene</td>
<td>-88</td>
<td>13</td>
<td>-70</td>
</tr>
<tr>
<td>6 Hexane</td>
<td>-80</td>
<td>14 MeOH</td>
<td>-13</td>
</tr>
<tr>
<td>7 THF</td>
<td>-70</td>
<td>15 Bn$_2$O</td>
<td>-82</td>
</tr>
<tr>
<td>8 EA</td>
<td>-76</td>
<td>16 Acetone</td>
<td>-45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 DME</td>
<td>-71</td>
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Table S4. Substrate Scope for Azodicarboxylates.
<table>
<thead>
<tr>
<th>Entry</th>
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<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DEAD</td>
<td>Et</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>DIAD</td>
<td>i-Pr</td>
<td>81</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>DTBAD</td>
<td>t-Bu</td>
<td>72</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>DCAD</td>
<td>p-Cl-Bn</td>
<td>83</td>
<td>59</td>
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<tr>
<td>5</td>
<td>PTAD</td>
<td><img src="product.png" alt="Product" /></td>
<td>52</td>
<td>0</td>
</tr>
</tbody>
</table>

**Mechanistic Studies (Table S5)**

While Tepe proposed a step-wise addition-cyclization mechanism for his un-catalyzed system, we found that the initial addition products could not undergo subsequent cyclization to give triazolines under his standard protocol. The primary addition product 3a was isolated and subjected under MeCN conditions. No reaction occurred (Table S5). The cyclization only occurred upon treatment with TMSCHN$_2$. This observation suggests that although our catalysed reactions proceeded through the step-wise, TMSCHN$_2$ promoted cyclization mechanism, the Tepe reaction was most likely a [3+2] cycloaddition for small size azodicarboxylates (DEAD and DIAD). When DTBAD was employed under the Tepe conditions, only the addition product was observed. Interception of 3a with electrophiles other than TMSCHN$_2$ was also attempted and the results are summarized in Table S5.
General Procedure for the Synthesis of 3-Quaternized 1,2,4-Triazolines:

One equivalent of the azodicarboxylate was added to a solution of azlactone rac-1 (0.1 mmol) and 5 mol% 7d in 1mL of ether in a 2-dram scintillation vial at room temperature. The reaction mixture was stirred at room temperature for 6 hours, which led to the disappearance of color. At this point the reaction mixture was cooled to 0 °C and (trimethylsilyl)diazomethane (2.0M solution in diethyl ether, 0.15 mL, 0.3 mmol, Caution: due to the potential explosive nature of this chemical, sharp objects should be avoided during handling and the reaction should be carried out behind a blast shield) was added in a drop wise manner. The reaction mixture was stirred for 15 minutes and methanol (0.3 mL) was added in drop wise manner. The reaction temperature was allowed to warm to ambient temperature. The progress of the reaction was monitored by TLC. About 6-24 hours later, the reaction mixture was concentrated to a minimal residue and purified by silica-gel flash chromatography to afford product 4.
Analytical Data and HPLC Chromatograms for 1,2,4-Triazolines Products:

![Chemical Structure]

Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4a):

81% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.84 – 7.79 (m, 1H), 7.49 (t, $J = 7.4$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 4.99 (dt, $J = 12.5$, 6.3 Hz, 1H), 4.88 (dt, $J = 12.5$, 6.2 Hz, 1H), 3.68 (s, 2H), 2.66 (dt, $J = 13.5$, 6.7 Hz, 1H), 1.31 (d, $J = 6.2$ Hz, 2H), 1.28 (d, $J = 6.3$ Hz, 2H), 1.11 (dd, $J = 6.4$, 4.8 Hz, 3H), 1.08 (d, $J = 6.2$ Hz, 2H), 0.96 (d, $J = 6.8$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 167.53, 158.45, 154.82, 152.01, 131.44, 129.55, 129.19, 127.70, 95.84, 77.24, 76.99, 76.74, 71.89, 70.76, 52.49, 33.49, 21.92, 21.71, 21.40, 21.36, 17.23, 16.28. HRMS (ESI) Calcd. for C$_{21}$H$_{30}$N$_3$O$_6$ ([M+H]$^+$): 420.2135; Found: 420.2131.

The ee was determined by HPLC using a Chiralcel OD-H column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; $t_R$major = 8.233 min, $t_R$minor = 6.906 min (93% ee). $^{24}$ [α]$_D$ = +84° (c = 0.1, CHCl$_3$).
Methyl 1,2-bis(isopropoxycarbonyl)-3-benzyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4b):

65% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.64 – 7.59 (m, 2H), 7.43 (t, $J = 7.5$ Hz, 1H), 7.34 (t, $J = 7.7$ Hz, 2H), 7.29 (d, $J = 7.3$ Hz, 2H), 7.21 (t, $J = 7.5$ Hz, 2H), 7.13 (t, $J = 7.3$ Hz, 1H), 5.03 (dt, $J = 12.5$, 6.2 Hz, 1H), 4.43 (dt, $J = 12.5$, 6.2 Hz, 1H), 3.76 (s, 3H), 3.63 (dd, $J = 14.1$ Hz, 1H), 3.43 (s, 3H), 1.35 (d, $J = 6.2$ Hz, 3H), 0.95 (d, $J = 6.3$ Hz, 3H), 0.73 (d, $J = 6.2$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 168.37, 159.16, 154.09, 150.54, 133.86, 131.24, 131.13, 129.43, 129.17, 127.61, 127.54, 126.76, 92.87, 77.30, 77.05, 76.79, 71.70, 70.76, 52.93, 41.18, 22.00, 21.68, 21.17, 21.02. HRMS (ESI) Calcd. for C$_{25}$H$_{30}$N$_{3}$O$_{6}$ ([M+H]$^+$): 468.2135; Found: 468.2142.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; $t_R$ major = 12.055 min, $t_R$ minor = 9.956 min (92% ee). $^{24b}$$[^{[\alpha]}_D = +105^\circ$ (c = 0.1, CHCl$_3$).
Methyl 1,2-bis(isopropoxycarbonyl)-3-isobutyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4c):

63% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.83 – 7.77 (m, 2H), 7.49 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 5.00 (dt, J = 12.5, 6.2 Hz, 1H), 4.88 (dt, J = 12.5, 6.2 Hz, 1H), 3.69 (s, 3H), 2.17 (d, J = 5.9 Hz, 2H), 1.82 – 1.76 (m, 1H), 1.30 (d, J = 6.2 Hz, 3H), 1.26 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H), 1.06 (d, J = 6.2 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.62, 158.64, 154.02, 152.13, 131.42, 129.62, 129.17, 127.68, 93.32, 77.26, 77.00, 76.75, 72.10, 70.60, 52.78, 43.31, 42.69, 23.78, 23.39, 21.93, 21.73, 21.34, 21.27. HRMS (ESI) Calcd. for C$_{22}$H$_{32}$N$_3$O$_6$ ([M+H]$^+$): 434.2291; Found: 434.2280.

The ee was determined by HPLC using a Chiralcel OJ column [n-hexane/EtOH (95:5)]; flow rate 1.0 mL/min; t$_{R}$major = 14.370 min, t$_{R}$minor = 4.951 min (90% ee). $^{24}$$^6$[α]$_D$ = +82° (c = 0.1, CHCl$_3$).
Methyl 1,2-bis(isopropoxycarbonyl)-3-allyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4d):

61% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.78 (d, $J = 7.3$ Hz, 2H), 7.49 (t, $J = 7.4$ Hz, 1H), 7.40 (t, $J = 7.7$ Hz, 2H), 5.69 (ddt, $J = 17.3$, 10.1, 7.3 Hz, 1H), 5.22 (d, $J = 17.2$ Hz, 1H), 5.11 (dd, $J = 10.2$, 1.5 Hz, 1H), 5.00 (dt, $J = 12.5$, 6.2 Hz, 1H), 4.85 (dq, $J = 12.5$, 6.2 Hz, 1H), 3.73 (s, 3H), 3.00 – 2.91 (m, 2H), 1.32 (d, $J = 6.2$ Hz, 3H), 1.28 (d, $J = 6.3$ Hz, 3H), 1.10 (d, $J = 6.2$ Hz, 3H), 1.06 (d, $J = 6.2$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.04, 159.45, 153.75, 151.86, 131.49, 130.60, 129.60, 129.11, 127.67, 120.66, 91.90, 77.25, 76.99, 76.74, 72.01, 70.74, 52.82, 39.24, 21.94, 21.72, 21.36. HRMS (ESI) Calcd. for C$_{21}$H$_{28}$N$_3$O$_6$ ([M+H]$^+$): 418.1978; Found: 418.1980.

The ee was determined by HPLC using IB column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; $t_R$major = 8.216 min, $t_R$minor = 7.612 min (86% ee). $^{24}$[α]$_D$ = +21° (c = 0.1, CHCl$_3$).
Methyl 1,2-bis(isopropoxycarbonyl)-3-(2-(methylthio)ethyl)-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4e):

78% yield, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.80 (d, $J = 7.6$ Hz, 2H), 7.50 (t, $J = 7.4$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 2H), 4.99 (dt, $J = 12.5$, 6.3 Hz, 1H), 4.87 (dt, $J = 12.4$, 6.2 Hz, 1H), 3.71 (s, 3H), 2.64–2.45 (m, 4H), 2.11 (s, 3H), 1.31 (d, $J = 6.2$ Hz, 3H), 1.13 (d, $J = 6.2$ Hz, 3H), 1.02 (d, $J = 6.2$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.04, 159.52, 153.81, 152.02, 131.69, 129.85, 128.91, 127.74, 92.22, 77.39, 77.07, 76.75, 72.43, 70.98, 52.99, 34.93, 27.79, 22.00, 21.96, 21.79, 21.53, 21.30, 15.50, 0.99. HRMS (ESI) Calcd. for C$_{21}$H$_{30}$N$_3$O$_6$S ([M+H]$: 452.1855$; Found: 452.1845$.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/MeOH (99:1)]; flow rate 1.0 mL/min; $t_{R}$major = 9.806 min, $t_{R}$minor = 11.572 min (87% ee). $^{24}$[α]$_D$ = +33 $^\circ$ (c = 0.1, CHCl$_3$).
Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-p-tolyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4f):

83% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.72 (d, $J$ = 8.1 Hz, 2H), 7.21 (d, $J$ = 8.0 Hz, 2H), 4.97 (dd, $J$ = 12.5, 6.2 Hz, 1H), 4.89 (dt, $J$ = 12.5, 6.2 Hz, 1H), 3.68 (s, 3H), 2.64 (dt, $J$ = 13.4, 6.7 Hz, 1H), 2.39 (s, 3H), 1.30 (d, $J$ = 6.2 Hz, 3H), 1.27 (d, $J$ = 6.3 Hz, 3H), 1.14 – 1.09 (m, 9H), 0.94 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.62, 158.44, 154.85, 152.15, 142.00, 129.62, 128.39, 126.20, 95.70, 77.25, 76.99, 76.74, 71.83, 70.69, 52.46, 33.50, 21.93, 21.71, 21.46, 21.41, 17.25, 16.27. HRMS (ESI): Calcd. for C$_{22}$H$_{32}$N$_3$O$_6$ ([M+H]$^+$): 434.2291; Found: 434.2277.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; t$_R$major = 8.197 min, t$_R$minor = 6.466 min (91% ee). $^{24,6}$$[\alpha]_D = +44$° (c = 0.1, CHCl$_3$).
Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-o-toly-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4g):

94% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.52 – 7.42 (m, 1H), 7.35 (td, $J = 7.6, 0.9$ Hz, 1H), 7.25 – 7.16 (m, 2H), 4.99 (dt, $J = 12.5, 6.2$ Hz, 1H), 4.82 (dt, $J = 12.4, 6.2$ Hz, 1H), 3.72 (s, 3H), 2.69 (dt, $J = 13.5, 6.7$ Hz, 1H), 2.47 (d, $J = 6.6$ Hz, 3H), 1.28 (dd, $J = 13.2, 6.2$ Hz, 7H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.05 – 1.01 (m, 6H), 0.94 (d, $J = 6.2$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 167.57, 157.72, 155.10, 150.78, 137.53, 130.45, 130.14, 129.08, 129.08, 125.36, 96.13, 77.23, 76.97, 76.72, 71.43, 70.80, 52.51, 33.44, 21.91, 21.69, 21.24, 21.14, 19.55, 17.21, 16.45. HRMS (ESI) Calcd. for C$_{22}$H$_{32}$N$_3$O$_6$ ([M+H]$^+$): 434.2291; Found: 434.2274.

The ee was determined by HPLC using IA column [n-hexane/EtOH (99:1)]; flow rate 0.3 mL/min; t$_R$major = 22.943 min, t$_R$minor = 24.887 min (90% ee). $^{24}$[$\alpha$]$_D$ = +79° (c = 0.1, CHCl$_3$).

**Table 1**

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Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(4-methoxyphenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4h):

67% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.78 (d, $J = 8.7$ Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 1H), 4.97 (dt, $J = 12.4, 6.2$ Hz, 1H), 4.89 (dt, $J = 12.4, 6.2$ Hz, 1H), 3.83 (s, 2H), 3.67 (s, 2H), 2.62 (dt, $J = 13.0, 6.3$ Hz, 1H), 1.29 (d, $J = 6.2$ Hz, 2H), 1.26 (d, $J = 6.3$ Hz, 2H), 1.16 – 1.08 (m, 5H), 0.93 (d, $J = 6.8$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.70, 162.38, 158.01, 154.85, 152.23, 131.56, 121.19, 113.13, 95.53, 77.26, 77.00, 76.75, 71.87, 70.73, 55.31, 52.46, 33.50, 21.90, 21.70, 21.48, 21.44, 17.24, 16.27. HRMS (ESI) Calcd. for C$_{22}$H$_{32}$N$_3$O$_7$ ([M+H]$^+$): 450.2240; Found: 450.2216.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; $t$$_R$ major = 13.134 min, $t$$_R$ minor = 10.925 min (90% ee). $^{27}$$[^a]$D = +48$^{10}$ (c = 0.1, CHCl$_3$).

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Electronic Supplementary Material (ESI) for Chemical Communications
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Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(3,5-dimethoxyphenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4i):

95% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.89 (d, $J = 2.3$ Hz, 2H), 6.54 (t, $J = 2.3$ Hz, 1H), 4.93 (dt, $J = 12.5, 6.3$ Hz, 1H), 4.84 (dt, $J = 12.4, 6.2$ Hz, 1H), 3.76 (s, 6H), 3.63 (s, 3H), 2.59 (dt, $J = 13.4, 6.7$ Hz, 1H), 1.25 (d, $J = 6.2$ Hz, 3H), 1.22 (d, $J = 6.3$ Hz, 3H), 1.09 - 1.03 (m, 9H), 0.89 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 167.48, 160.19, 158.42, 154.81, 151.97, 130.84, 107.56, 103.89, 95.83, 77.44, 77.18, 76.93, 71.91, 70.80, 55.46, 52.52, 33.44, 21.90, 21.70, 21.43, 21.40, 17.26, 16.26. HRMS (ESI) Calcd. for C$_{23}$H$_{34}$N$_3$O$_8$ ([M+H]$^+$): 480.2346; Found: 480.2353.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; $t_{R}$ major = 12.116 min, $t_{R}$ minor = 8.655 min (92% ee). $^{27}$[α]$_D$ = +36 ° (c = 0.1, CHCl$_3$).
Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(naphthalen-1-yl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4j):

91% yield, colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.40 (d, \(J = 8.4\) Hz, 1H), 7.97 (d, \(J = 8.3\) Hz, 1H), 7.87 (d, \(J = 8.0\) Hz, 1H), 7.80 (dd, \(J = 7.0, 0.7\) Hz, 1H), 7.58 – 7.47 (m, 3H), 5.07 (dt, \(J = 12.5, 6.2\) Hz, 1H), 4.67 (dt, \(J = 12.4, 6.2\) Hz, 1H), 3.74 (s, 3H), 2.78 (dt, \(J = 13.4, 6.7\) Hz, 1H), 1.38 (d, \(J = 6.2\) Hz, 3H), 1.32 (d, \(J = 6.3\) Hz, 3H), 1.21 (d, \(J = 6.8\) Hz, 3H), 1.11 (d, \(J = 6.8\) Hz, 3H), 0.73 (d, \(J = 6.2\) Hz, 3H), 0.68 (d, \(J = 6.2\) Hz, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 167.57, 157.31, 155.26, 150.64, 133.16, 131.46, 131.31, 128.20, 128.01, 127.33, 127.06, 126.15, 124.94, 124.54, 96.31, 77.24, 76.99, 76.73, 71.37, 70.94, 52.62, 33.59, 22.01, 21.75, 20.97, 20.85, 17.31, 16.53. HRMS (ESI) Calcd. for C\(_{25}\)H\(_{31}\)N\(_3\)O\(_6\)Na\(^{[M+Na]^+}\): 492.2111; Found: 492.2082.

The ee was determined by HPLC using IA column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; \(t_\text{R}\)major = 8.237 min, \(t_\text{R}\)minor = 9.317 min (90% ee). \(^{27}\)\(\text{[a]}\)D = +78 \(^\circ\) (c = 0.1, CHCl\(_3\)).
Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(naphthalen-2-yl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4k):

93% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.38 (s, 1H), 7.89 (ddd, $J$ = 13.5, 12.9, 8.5 Hz, 4H), 7.58 – 7.51 (m, 2H), 5.03 (dt, $J$ = 12.5, 6.3 Hz, 1H), 4.90 (dt, $J$ = 12.5, 6.2 Hz, 1H), 3.70 (s, 3H), 2.73 (dt, $J$ = 13.5, 6.7 Hz, 1H), 1.35 (d, $J$ = 6.2 Hz, 3H), 1.31 (d, $J$ = 6.3 Hz, 3H), 1.17 (d, $J$ = 6.8 Hz, 3H), 1.08 (d, $J$ = 6.2 Hz, 3H), 1.06 (d, $J$ = 6.2 Hz, 3H), 1.03 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 167.58, 158.59, 154.85, 152.12, 134.80, 130.25, 128.79, 127.68, 127.63, 127.27, 126.52, 126.40, 126.05, 95.94, 77.23, 76.97, 76.72, 71.98, 70.83, 52.52, 33.58, 21.95, 21.74, 21.41, 21.38, 17.31, 16.37. HRMS (ESI) Calcd. for C$_{25}$H$_{32}$N$_3$O$_6$ ([M+H]$^+$): 470.2291; Found: 470.2280.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; t$_R$major = 10.344 min, t$_R$minor = 7.788 min (93% ee). $^{27,8}$$[\alpha]_D$ = +62$^\circ$ (c = 0.1, CHCl$_3$).
Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4l):

66% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, $J$ = 8.0 Hz, 2H), 7.71 (d, $J$ = 8.2 Hz, 2H), 5.02 (dd, $J$ = 12.5, 6.2 Hz, 1H), 4.93 (dt, $J$ = 12.4, 6.2 Hz, 1H), 3.73 (s, 3H), 2.76–2.64 (m, 1H), 1.34 (d, $J$ = 6.2 Hz, 3H), 1.31 (d, $J$ = 6.3 Hz, 3H), 1.15 (t, $J$ = 6.2 Hz, 9H), 0.98 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.28, 157.42, 154.82, 152.01, 133.39, 133.13, 132.68, 130.02, 124.79, 122.59, 72.37, 71.05, 52.66, 33.54, 21.96, 21.75, 21.46, 17.26, 16.34. HRMS (ESI) Calcd. for C$_{22}$H$_{28}$F$_3$N$_3$O$_6$Na([M+Na]$: 510.1828; Found: 510.1817.

The ee was determined by HPLC using Chiralpak AD-H column [n-hexane/EtOH (97.5:2.5)]; flow rate 1.0 mL/min; $t_R$ major = 4.386 min, $t_R$ minor = 6.285 min (92% ee). $^{27a}[\alpha]_0 = +87^\circ$ (c = 0.1, CHCl$_3$).
Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(4-chlorophenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4m):  
75% yield, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.77 (dd, $J = 4.6, 4.0$ Hz, 2H), 7.38 (dd, $J = 8.6, 1.2$ Hz, 2H), 4.98 (dd, $J = 12.3, 6.2$ Hz, 1H), 4.89 (dt, $J = 12.4, 6.2$ Hz, 1H), 3.68 (s, 1H), 2.64 (dt, $J = 13.1, 6.5$ Hz, 1H), 1.30 (d, $J = 6.2$ Hz, 3H), 1.27 (d, $J = 6.4$ Hz, 3H), 1.16 – 1.09 (m, 9H), 0.93 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.42, 157.59, 154.83, 152.07, 137.85, 131.04, 128.10, 127.52, 95.94, 77.39, 77.08, 76.76, 72.25, 70.95, 52.65, 33.50, 21.97, 21.76, 21.52, 21.48, 17.29, 16.30. HRMS (ESI) Calcd. for C$_{21}$H$_{29}$ClN$_3$O$_6$([M+H]$^+$): 454.1745; Found: 454.1728.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; $t_{R}$major = 6.919 min, $t_{R}$minor = 5.780 min (90% ee). $^{27.8}$$[\alpha]_D^0 = +80 \degree$ (c = 0.1 ,
Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(3-chlorophenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4n):
77% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.82 (t, $J$ = 1.7 Hz, 1H), 7.72 (dd, $J$ = 6.7, 1.1 Hz, 1H), 7.48 (dd, $J$ = 7.9, 1.9, 0.9 Hz, 1H), 7.36 (t, $J$ = 7.9 Hz, 1H), 4.99 (dd, $J$ = 12.5, 6.2 Hz, 1H), 4.90 (dd, $J$ = 12.5, 6.2 Hz, 1H), 3.70 (s, 3H), 2.66 (dd, $J$ = 13.5, 6.7 Hz, 1H), 1.31 (d, $J$ = 6.2 Hz, 3H), 1.28 (d, $J$ = 6.3 Hz, 3H), 1.14 (d, $J$ = 6.2 Hz, 3H), 1.11 (dd, $J$ = 6.5, 1.7 Hz, 6H), 0.95 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 167.31, 157.27, 154.73, 151.84, 133.83, 131.47, 130.84, 129.58, 129.01, 127.78, 95.99, 77.20, 76.95, 76.69, 72.21, 70.94, 52.58, 33.47, 21.91, 21.70, 21.42, 17.20, 16.29. HRMS (ESI) Calcd. for C$_{21}$H$_{38}$Cl$_3$N$_2$O$_6$Na ([M+Na]$^+$): 476.1564; Found: 476.1557.

The ee was determined by HPLC using a Chiralcel OJ column [n-hexane/EtOH (98:2)]; flow
rate 1.0 mL/min; $t_R$ major $= 8.047$ min, $t_R$ minor $= 6.103$ min (92% ee). $^{27.8} \lbrack \alpha \rbrack_D = +94^{\circ}$ (c = 0.1, CHCl$_3$).

Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(4-bromophenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4o):
65% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.70 (d, $J$ = 8.2 Hz, 2H), 7.55 (d, $J$ = 8.1 Hz, 2H), 4.98 (dd, $J$ = 12.3, 6.2 Hz, 1H), 4.89 (dt, $J$ = 12.4, 6.2 Hz, 1H), 3.69 (s, 3H), 2.64 (dt, $J$ = 13.2, 6.5 Hz, 1H), 1.30 (d, $J$ = 6.2 Hz, 3H), 1.27 (d, $J$ = 6.4 Hz, 3H), 1.16 − 1.09 (m, 9H), 0.93 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.34, 157.62, 154.75, 154.72, 154.02, 131.13, 131.02, 128.00, 126.20, 95.96, 77.24, 76.98, 76.73, 72.18, 70.87, 52.55, 33.45, 21.90, 21.69, 21.46, 21.42, 17.21, 16.27. HRMS (ESI) Calcd. for C$_2$H$_{35}$BrN$_5$O$_6$ ([M+H]^+): 498.1240; Found: 498.1243.

The ee was determined by HPLC using Chiralpak AD-H column [n-hexane/EtOH (98:2)]; flow rate 1.0 mL/min; $t_R$ major $= 7.492$ min, $t_R$ minor $= 10.924$ min (91% ee). $^{27.8} \lbrack \alpha \rbrack_D = +83^{\circ}$ (c = 0.1, CHCl$_3$).
Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(3-fluoro-4-methylphenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4p):

87% yield, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.55 – 7.46 (m, 2H), 7.23 (t, J = 7.7 Hz, 1H), 4.98 (dt, J = 12.6, 6.3 Hz, 1H), 4.91 (dt, J = 12.5, 6.3 Hz, 1H), 3.69 (s, 3H), 2.64 (dt, J = 13.4, 6.7 Hz, 1H), 2.32 (s, 3H), 1.29 (dd, J = 10.7, 6.3 Hz, 6H), 1.15 (dd, J = 6.2, 4.3 Hz, 6H), 1.11 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.49, 161.67, 159.23, 157.52, 154.87, 152.14, 130.83, 130.78, 129.09, 128.37, 128.29, 125.28, 125.24, 116.45, 116.20, 95.87, 77.35, 77.04, 76.72, 72.16, 70.91, 52.62, 33.52, 21.98, 21.77, 21.52, 21.50, 17.28, 16.32, 14.72, 14.69. ¹⁹F NMR (376 MHz, CDCl₃) δ -117.51. HRMS (ESI) Calcd. for C₂₂H₃₁F₃N₃O₆ ([M+H]⁺): 452.2197; Found: 452.2200.
The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; $t_{R}$major = 9.621 min, $t_{R}$minor = 7.885 min (90% ee). $^{27.8}\[\alpha\]_{D}^{27.8} = +67\degree$ (c = 0.1, CHCl$_3$).

Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(4-fluorophenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4q):
65% yield, colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.55 – 7.46 (m, 2H), 7.23 (t, $J = 7.7$ Hz, 1H), 4.98 (dt, $J = 12.6, 6.3$ Hz, 1H), 4.91 (dt, $J = 12.5, 6.3$ Hz, 1H), 3.69 (s, 3H), 2.64 (dt, $J = 13.4, 6.7$ Hz, 1H), 2.32 (s, 3H), 1.29 (dd, $J = 10.7, 6.3$ Hz, 6H), 1.15 (dd, $J = 6.2, 4.3$ Hz, 6H), 1.11 (d, $J = 6.8$ Hz, 3H), 0.94 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.49, 161.67, 159.23, 157.52, 154.87, 152.14, 130.83, 130.78, 129.09, 128.91, 128.37, 125.28, 125.24, 116.45, 116.20, 95.87, 77.35, 77.04, 76.72, 72.16, 70.91, 52.62, 33.52, 21.98, 21.77, 21.52, 21.50, 17.28, 16.32, 14.72, 14.69. HRMS (ESI) Calcd. for C$_{21}$H$_{29}$FN$_3$O$_6$ ([M+H]$^+$): 438.2040; Found: 438.2048.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow...
rate 1.0 mL/min; \( t_{R} \) major = 10.465 min, \( t_{R} \) minor = 8.731 min (90% ee). \( ^{27\theta} \alpha \) = +77 ° (c = 0.1, CHCl₃).

27.8 \( \alpha \) = +77° (c = 0.1, CHCl₃).

Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(3-cyanophenyl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4r): 51% yield, colorless oil. \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 8.14 (s, 1H), 8.08 (d, \( J = 7.9 \) Hz, 1H), 7.79 (d, \( J = 7.7 \) Hz, 1H), 7.56 (t, \( J = 7.8 \) Hz, 1H), 5.03 – 4.99 (m, 1H), 4.91 (dd, \( J = 12.4, 6.2 \) Hz, 1H), 3.71 (s, 3H), 2.68 (dt, \( J = 13.0, 6.4 \) Hz, 1H), 1.33 (d, \( J = 6.2 \) Hz, 3H), 1.30 (d, \( J = 6.3 \) Hz, 3H), 1.16 (t, \( J = 5.8 \) Hz, 6H), 1.12 (d, \( J = 6.7 \) Hz, 3H), 0.96 (d, \( J = 6.8 \) Hz, 3H). \(^{13}\)C NMR (126 MHz, CDCl₃) \( \delta \) 167.12, 156.65, 154.73, 151.90, 134.51, 133.68, 133.25, 130.51, 128.66, 117.74, 112.45, 96.27, 77.17, 76.92, 76.66, 72.50, 71.11, 52.63, 33.48, 21.90, 21.68, 21.47, 21.43, 17.16, 16.31. HRMS (ESI) Calcd. for C₂₂H₂₈N₄O₆Na ([M+Na]⁺): 467.1907; Found: 467.1895.

The ee was determined by HPLC using IA column [n-hexane/EOH (97.5:2.5)]; flow rate 1.0 mL/min; \( t_{R} \) major = 12.925 min, \( t_{R} \) minor = 11.036 min (90% ee). \( ^{27\theta} \alpha \) = +16° (c = 0.1, CHCl₃).
Methyl 1,2-bis(isopropoxycarbonyl)-3-isopropyl-5-(6-methoxypyridin-3-yl)-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4s):

50% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.63 (s, 1H), 8.02 – 7.95 (m, 1H), 6.77 – 6.71 (m, 1H), 4.99 – 4.94 (m, 1H), 4.92 – 4.86 (m, 1H), 3.97 (d, $J$ = 1.7 Hz, 1H), 3.68 (d, $J$ = 1.5 Hz, 1H), 2.61 (dd, $J$ = 12.8, 6.3 Hz, 1H), 1.29 – 1.25 (m, 6H), 1.18 – 1.13 (m, 6H), 1.08 (d, $J$ = 6.6 Hz, 3H), 0.91 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.47, 165.99, 156.02, 154.74, 152.04, 149.09, 139.62, 118.37, 109.79, 95.68, 77.24, 76.98, 76.73, 72.14, 70.79, 53.76, 52.48, 33.49, 21.88, 21.67, 21.49, 21.44, 17.17, 16.26. HRMS (ESI) Calcd. for C$_{21}$H$_{31}$N$_4$O$_7$ ([M+H]$: 451.2193; Found: 451.2178.

The ee was determined by HPLC using IA column [n-hexane/EtOH (99:1)]; flow rate 0.5
mL/min; $t_{\text{major}} = 25.889$ min, $t_{\text{minor}} = 23.540$ min (90% ee). $^{27} \beta [\alpha]_D = +46^\circ$ (c = 0.1, CHCl$_3$).

Methyl 1,2-bis(isopropoxycarbonyl)-3-benzyl-5-cyclopropyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4t):
82% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.24 – 7.15 (m, 3H), 7.13 (d, $J = 7.7$ Hz, 2H), 4.97 (dt, $J = 12.5, 6.2$ Hz, 1H), 4.77 (dt, $J = 12.5, 6.2$ Hz, 1H), 3.77 (s, 3H), 3.43 (d, $J = 14.0$ Hz, 1H), 3.30 (d, $J = 14.0$ Hz, 1H), 2.04 – 1.97 (m, 1H), 1.32 (d, $J = 6.2$ Hz, 3H), 1.25 (d, $J = 6.3$ Hz, 4H), 1.21 (d, $J = 6.3$ Hz, 3H), 1.15 (d, $J = 6.2$ Hz, 3H), 0.91 – 0.85 (m, 1H), 0.80 – 0.73 (m, 1H), 0.52 – 0.46 (m, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.82, 161.87, 154.09, 150.35, 134.09, 131.25, 127.44, 126.60, 92.08, 77.21, 76.96, 76.71, 71.53, 70.67, 52.79, 41.11, 21.98, 21.65, 21.61, 21.49, 10.09, 9.70, 8.29. HRMS (ESI) Calcd. for C$_{22}$H$_{30}$N$_3$O$_6$ ([M+H]$^+$): 432.2135; Found: 432.2131.

The ee was determined by HPLC using IA column [n-hexane/EtOH (99:1)]; flow rate 1.0...
mL/min; $t_{R_{\text{major}}} = 9.750 \text{ min}, t_{R_{\text{minor}}} = 11.260 \text{ min (81% ee)}. \quad [\alpha]_D = +12^\circ \ (c = 0.1, \text{ CHCl}_3)$.

Methyl 1,2-bis(isopropoxycarbonyl)-3-(4-bromophenyl)-5-[[1,1'-biphenyl]-4-yl]-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (4u):

42% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.74 (d, $J = 8.4 \text{ Hz}, 2H), 7.64 - 7.57 \ (m, 4H), 7.46 \ (t, J = 7.6 \text{ Hz}, 2H), 7.38 \ (dd, J = 15.6, 7.9 \text{ Hz}, 3H), 7.19 \ (d, J = 8.4 \text{ Hz}, 2H), 5.05 \ (dt, J = 12.5, 6.2 \text{ Hz}, 1H), 4.53 \ (dt, J = 12.4, 6.2 \text{ Hz}, 1H), 3.78 \ (s, 3H), 3.60 \ (d, J = 14.1 \text{ Hz}, 1H), 3.43 \ (d, J = 14.1 \text{ Hz}, 1H), 1.36 \ (d, J = 6.2 \text{ Hz}, 3H), 1.30 \ (d, J = 6.3 \text{ Hz}, 3H), 0.99 \ (d, J = 6.2 \text{ Hz}, 3H), 0.81 \ (d, J = 6.2 \text{ Hz}, 3H). \quad ^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 168.26, 159.36, 150.73, 144.38, 140.10, 133.07, 132.99, 130.86, 129.85, 128.94, 128.04, 127.20, 126.38, 121.13, 92.59, 72.35, 71.01, 53.18, 40.67, 22.13, 21.81, 21.34, 21.24. HRMS (ESI) Calcd. for C$_{33}$H$_{33}$BrN$_3$O$_6$ ([M+H]+): 622.1553; Found: 622.1547.
The ee was determined by HPLC using AD column [n-hexane/EtOH (95:5)]; flow rate 1.0 mL/min; t<sub>R</sub>major = 10.399 min, t<sub>R</sub>minor = 14.044 min (93% ee). 27.8°[α]<sub>d</sub> = +74° (c = 0.1, CHCl<sub>3</sub>).

Methyl 1,2-bis(ethoxycarbonyl)-3-isopropyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (DEAD-product):

90% yield, colorless oil. 1H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.85 – 7.80 (m, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.7 Hz, 2H), 4.31 – 4.24 (m, 1H), 4.23 – 4.09 (m, 3H), 3.70 (s, 3H), 2.67 (dt, J = 13.5, 6.7 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.10 (dd, J = 13.9, 6.9 Hz, 6H), 0.97 (d, J = 6.8 Hz, 3H); 13C NMR (126 MHz, CDCl<sub>3</sub>) δ 167.46, 158.30, 155.35, 152.52, 131.57, 129.55, 128.93, 127.76, 96.10, 77.24, 76.98, 76.73, 63.55, 62.68, 52.60, 33.53, 17.13, 16.31, 14.19, 13.80.

HRMS (ESI) Calcd. for C<sub>19</sub>H<sub>26</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>): 392.1822; Found: 392.1820.
The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; \( t_R \) major = 14.941 min, \( t_R \) minor = 10.307 min (90% ee). \( ^{27} \alpha \) = +61 ° (c = 0.1, CHCl₃).

Methyl 1,2-bis(tertbutoxycarbonyl)-3-isopropyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (DTBAD-product):
72% yield, colorless oil. \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 7.80 (d, \( J = 7.7 \) Hz, 2H), 7.48 (t, \( J = 7.4 \) Hz, 1H), 7.40 (t, \( J = 7.6 \) Hz, 2H), 3.68 (s, 3H), 2.63 (dt, \( J = 13.3, 6.6 \) Hz, 1H), 1.50 (s, 9H), 1.28 (s, 9H), 1.13 (d, \( J = 6.7 \) Hz, 3H), 0.97 (d, \( J = 6.8 \) Hz, 3H); \(^{13}\)C NMR (126 MHz, CDCl₃) \( \delta \) 167.78, 158.73, 153.80, 150.84, 131.21, 129.44, 128.37, 127.73, 95.21, 83.75, 82.30, 77.22, 76.97, 76.71, 52.37, 33.54, 28.01, 27.56, 17.23, 16.29. HRMS (ESI) Calcd. for C₂₃H₂₄N₂O₆ ([M+H]⁺): 448.2448; Found: 448.2487.

The ee was determined by HPLC using a Chiralcel OD column [n-hexane/EtOH (99:1)]; flow rate 0.5 mL/min; \( t_R \) major = 12.183 min, \( t_R \) minor = 8.688 min (90% ee). \( ^{27} \alpha \) = +66 ° (c = 0.1, CHCl₃).
Methyl 1,2-bis(4-chlorobenzyloxy carbonyl)-3-isopropyl-5-phenyl-2,3-dihydro-1H-1,2,4-triazole-3-carboxylate (DCAD-product):

83% yield, colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.83 – 7.77 (m, 2H), 7.51 (t, $J = 7.4$ Hz, 1H), 7.40 (t, $J = 7.7$ Hz, 2H), 7.32 (q, $J = 8.5$ Hz, 4H), 7.22 (d, $J = 8.3$ Hz, 2H), 6.95 (d, $J = 8.3$ Hz, 2H), 5.21 (d, $J = 12.4$ Hz, 1H), 5.12 (d, $J = 12.4$ Hz, 1H), 5.05 (q, $J = 12.4$ Hz, 2H), 3.51 (s, 3H), 3.25 (dt, $J = 13.2$, 6.5 Hz, 1H), 1.06 (d, $J = 6.8$ Hz, 3H), 0.90 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.16, 157.88, 155.15, 152.34, 134.40, 134.34, 133.83, 132.82, 131.76, 129.60, 129.50, 129.27, 128.70, 128.60, 127.98, 96.38, 77.27, 77.02, 76.76, 68.30, 67.51,
52.63, 33.46, 17.15, 16.27. HRMS (ESI) Calcd. for C_{29}H_{26}Cl_{2}N_{3}O_{6} ([M+H]^+): 584.1355; Found: 584.1344.

The ee was determined by HPLC using a Chiralcel IA column [n-hexane/EtOH (95:5)]; flow rate 1.0 mL/min; t_R major = 13.711 min, t_R minor = 16.931 min (59% ee).^{27}[α]_D = +46° (c = 0.1, CHCl₃).

Methyl 1-isopropyl-5,7-dioxo-3,6-diphenyl-1,5,6,7-tetrahydro-[1,2,4]triazolo[1,2-a][1,2,4]triazole-1-carboxylate (PTAD-product):
52% yield, colorless oil. \(^1\)H NMR (500 MHz, CDCl₃) δ 8.13 – 8.07 (m, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.49 (q, J = 8.2 Hz, 6H), 7.43 – 7.39 (m, 1H), 3.85 (s, 3H), 2.92 (dt, J = 13.5, 6.8 Hz, 1H), 1.25 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H); \(^13\)C NMR (126 MHz, CDCl₃) δ 166.52, 153.75, 153.61, 148.69, 133.13, 131.01, 131.39, 129.16, 128.80, 128.27, 126.08, 125.04, 98.09, 77.25, 77.00, 76.75, 53.46, 33.08, 17.56, 16.11. HRMS (ESI) Calcd. for C_{21}H_{20}N_{4}O_{4} ([M+H]^+): 393.1563; Found: 393.1555.

The ee was determined by HPLC using a Chiralcel IA column [n-hexane/EtOH (99:1)]; flow
rate 1.0 mL/min; $t_R^{\text{major}} = 10.263$ min, $t_R^{\text{minor}} = 11.746$ min (2% ee). $^{27}$[α]$^D = +18^\circ$ (c = 0.1, CHCl₃).
Derivatization and Characterization of Triazoline Products

Three equivalents of LiI was added to a solution of 4a in EA and refluxed overnight. The progress of the reaction was monitored by TLC. The reaction was washed three times with aqueous NH₄Cl solution and dried over Na₂SO₄. The volatile solvent was removed and the product 8 was used directly without further purification.

A solution of 8, EDCI (2 equiv.), and HOAT (2 equiv.) in dry dichloromethane was cooled to 0°C, and followed this, DIPEA (8 equiv.) was added. After the reaction mixture was stirred for 5 min, the amine (1.5 equiv.) was added dropwise. The progress of the reaction was monitored by TLC.

Upon complete consumption of the starting material 8, the reaction was washed three times with aqueous NaHCO₃ solution and dried over Na₂SO₄. The volatile solvent was removed and the product was purified by silica gel flash chromatography (ethyl acetate / hexane).

Isopropyl 7a-isopropyl-6-((S)-1-methoxy-1-oxopropan-2-yl)-5,7-dioxo-2-phenyl-5,6,7,7a-tetrahydro-3H-imidazo[1,5-b][1,2,4]triazole-3-carboxylate (9a):

85% yield, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.89 – 7.81 (m, 2H), 7.53 (dd, J = 10.6, 4.3 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 4.99 (dt, J = 12.5, 6.2 Hz, 1H), 4.79 (q, J = 7.3 Hz, 1H), 3.71 (s, 3H), 2.52 (dd, J = 13.8, 6.9 Hz, 1H), 1.66 – 1.62 (m, 3H), 1.21 (d, J = 6.2 Hz, 3H), 1.16 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 169.75, 168.77, 161.29, 160.18, 152.40, 132.15, 129.81, 128.35, 127.97, 96.25, 77.17, 76.92, 76.67, 72.49, 52.68, 49.05, 32.04, 29.30, 21.52, 21.41, 16.07, 14.92, 14.38. HRMS (ESI) Calcd. for C₂₁H₂₇N₄O₆([M+H]⁺): 431.1931; Found: 431.1932.

The ee was determined by HPLC using IA column [n-hexane/EtOH (97.5:2.5)]; flow rate 1.0 mL/min; tₘajor = 8.898 min, tₘinor = 10.609 min (92% ee). ²⁷°[α]D = +136° (c = 0.1, CHCl₃).
Isopropyl 6-((S)-3-hydroxy-1-methoxy-1-oxopropan-2-yl)-7a-isopropyl-5,7-dioxo-2-phenyl-5,6,7,7a-tetrahydro-3H-imidazo[1,5-b][1,2,4]triazole-3-carboxylate (9b):

83% yield, colourless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.89 – 7.82 (m, 2H), 7.55 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 2H), 5.00 (dt, $J = 12.3$, 6.2 Hz, 1H), 4.89 (dt, $J = 9.3$, 4.8 Hz, 1H), 4.15 (ddddd, $J = 14.9$, 12.4, 9.2 Hz, 2H), 3.79 (d, $J = 4.0$ Hz, 3H), 2.54 (ddd, $J = 14.7$, 7.7 Hz, 1H), 1.22 (dd, $J = 6.1$, 2.1 Hz, 3H), 1.18 (dd, $J = 6.1$, 3.6 Hz, 3H), 1.14 (dd, $J = 16.9$, 6.8 Hz, 3H), 0.95 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.96, 170.61, 167.13, 167.09, 162.18, 161.64, 160.41, 160.37, 152.34, 132.31, 129.95, 129.88, 128.26, 128.05, 128.03, 96.40, 96.37, 72.69, 60.33, 60.28, 60.10, 56.20, 53.03, 52.88, 52.33, 32.17, 21.56, 21.46, 16.18, 16.15, 14.95.

HRMS (ESI) Calcd. for C$_{21}$H$_{27}$N$_4$O$_7$ ([M+H]$^+$): 447.1880; Found: 447.1875.

The ee was determined by HPLC using IA column [n-hexane/ EtOH (95:5)]; flow rate 1.0 mL/min; $t_r$ major = 22.344 min, $t_r$ minor = 25.584 min (91% ee). $^{27}$[α]$_D$ = +168° (c = 0.1, CHCl$_3$).
Isopropyl 6-butyl-7a-isopropyl-5,7-dioxo-2-phenyl-5,6,7,8a-tetrahydro-3H-imidazo[1,5-b][1,2,4]triazole-3-carboxylate (9c):

81% yield, colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.89 – 7.78 (m, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 4.98 (dt, J = 12.5, 6.2 Hz, 1H), 3.56 (td, J = 7.1, 4.6 Hz, 2H), 2.51 (dt, J = 13.7, 6.9 Hz, 1H), 1.61 (dd, J = 8.3, 5.2 Hz, 2H), 1.36 – 1.29 (m, 2H), 1.19 (d, J = 6.2 Hz, 3H), 1.15 (d, J = 6.2 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 0.92 (dd, J = 13.5, 7.1 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 170.73, 162.43, 160.20, 152.56, 132.17, 129.86, 128.45, 127.99, 96.21, 72.49, 39.32, 31.89, 29.56, 21.60, 21.47, 19.83, 16.29, 14.88, 13.49. HRMS (ESI) Calcd. for C₂₁H₂₉N₄O₄ [M+H]+: 401.2189; Found: 401.2187.

The ee was determined by HPLC using IA column [n-hexane/EtOH (99:1)]; flow rate 1.0 mL/min; tᵣmajor = 8.044 min, tᵣminor = 12.210 min (90% ee). [α]D = +81° (c = 0.1, CHCl₃).
Diisopropyl 3-((3,5-dimethoxyphenyl)carbamoyl)-3-isopropyl-5-phenyl-1H-1,2,4-triazole-1,2(3H)-dicarboxylate (9d):

85% yield, colourless oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.49 (s, 1H), 8.28 (d, $J = 9.5$ Hz, 1H), 7.94 (d, $J = 7.3$ Hz, 2H), 7.55 (d, $J = 7.4$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 2H), 6.47 (d, $J = 7.0$ Hz, 2H), 5.05 (dt, $J = 12.2$, 6.1 Hz, 1H), 4.83 (dt, $J = 12.3$, 6.1 Hz, 1H), 3.80 (d, $J = 6.9$ Hz, 6H), 3.19 (s, 1H), 1.34 (d, $J = 6.2$ Hz, 3H), 1.28 (d, $J = 5.4$ Hz, 3H), 1.17 (d, $J = 6.7$ Hz, 3H), 1.10 – 1.01 (m, 6H), 0.96 (d, $J = 4.8$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 165.57, 158.85, 156.55, 154.14, 151.87, 149.52, 131.63, 129.86, 129.19, 127.19, 127.0, 124.9, 121.10, 120.48, 103.91, 98.76, 96.45, 72.12, 70.82, 55.84, 55.50, 21.84, 21.82, 21.36, 21.29, 17.79, 16.19. HRMS (ESI) Calcd. for C$_{33}$H$_{37}$N$_4$O$_7$ ([M+H]+): 541.2662; Found: 541.2656.

The ee was determined by HPLC using IA column [n-hexane/ EtOH (97.5:2.5)]; flow rate 1.0 mL/min; $t_R$ major = 18.973 min, $t_R$ minor = 21.623 min (93% ee). $^2$H$_2$$^7$[α]$_D$ = +102 $^\circ$ (c = 0.1 ,
CHCl₃).
References

NMR Spectra Images

7d, 500MHz, CDCl₃

7d, 126MHz, CDCl₃
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4a, 400 MHz, CDCl₃

4g, 101 MHz, CDCl₃
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400MHz, CDCl₃

126MHz, CDCl₃
$^{1}H$, 500 MHz, CDCl$_3$

$^{13}C$, 126 MHz, CDCl$_3$
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